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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,712	EATON ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/28/05,9/17/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Claim Rejections - 35 USC §§ 101/112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a polynucleotide. The specification asserts a number of utilities for both the encoded polypeptide and encoding polynucleotide, however, these utilities are not specific and substantial or well established. An example of utility is in drug screening and rational drug design (Examples 12 and 13, respectively). The methods involve screening for "agents which can affect a PRO polypeptide-associated disease or disorder" [0507]. No disease or disorder is known to be associated with the claimed polynucleotide or encoded polypeptide. In order to discern a utility for the claimed polynucleotide through drug screening in the absence of guidance about which type of disease or disorder the polynucleotide or encoded polypeptide causes or how its involvement could lead to treatment, screening for drugs by using the polynucleotide or encoded polypeptide would still require further and undue experimentation to determine the significance of an agent that somehow influenced the polynucleotide's or polypeptide's function.

Another possible utility comes from the finding that the encoding polynucleotide encodes a polypeptide that stimulates TNF-α release in human blood (Assay 128, EXAMPLE 17, p. 139). This example does not provide a specific and substantial utility for a number of reasons. First, "A positive in the assay is a higher amount of TNF-α in the PRO polypeptide treated samples as compared to the negative control samples," [0527]. There is no statement as to the statistical significance of the data. The number of samples tested with the PRO 1356 polypeptide tested is

not disclosed. There is no information to allow the skilled artisan to conclude that the result in the specification is generally repeatable so that it would have a substantial utility. Further, even if PRO 1356 could be predictably used to release TNF-α from human blood, this in itself would not provide a specific or substantial utility. TNF-α has complex actions and interactions as discussed by Halle et al. (Exercise Immunol. Rev., 4:77, 1998, paragraph bridging pages 79-80):

> TNF-α is a cytokine that can be synthesized by several cell types and has been shown to be involved in physiological states such as inflammation, cytotoxicity, immunomodulation, cellular growth, and angiogenesis. It acts on immune cells by directly inducing the release of other cytkines such as interleukin-1 (IL-1) or granulocyte macrophage-colony-stimulating factor (GM-CSF), but has also been found to have several other effects … such as influence on lipid metabolism and adhesion of leukocytes to endothelial cells…. In addition TNF-α together with other cytkines such as IL-1 is also involved in thermogenesis of brown adipose tissue. The effect of TNF-α is mediated by the binding of TNF-α to two distinct receptors—the TNF-α-R55 and TNF-α-R80—the former being responsible fo the cytotoxic activity of TNF-α in general as well as the TNF-α insulin resistance….

Tsimberidou et al. (Expert Rev. Anticancer Ther. 2(3):277, 2002, p. 277, second paragraph) discusses that, "TNF-α is involved in the pathogenesis of hematologic malignancies, such as multiple myeloma…, myelodysplastic syndrome…, acute myelogenous leukemia…, and also conditions associated with the use of allogeneic stem cell transplantation for their treatment, such as graft *versus* host disease…." As can be seen from these two references, which a plethora of other could be cited to support, TNF-α has many undesirable physiological effects. On the other hand, Lackie et al. in The Dictionary of Cell and Molecular Biology (p. 476) have as part of the definition of TNF-α (also called cachectin) that it "Preferentially kills tumour cells *in vivo* and *in vitro*, causing necrosis of certain transplanted tumours in mice and inhibits experimental metastases." Even though it might have potential therapeutic anti-tumor benefit, which tumors it can effect, how it can be administered without the undesirable non-tumor cytotoxic activity outweighing the benefits of anti-tumor effects, how the side effects such as inflammation can be handled, and finally, how the leap can be made from release of TNF-α from blood to having a particular therapeutic benefit with the above considerations taken together, is far from clear with the guidance and examples in the specification or prior art. As a result, the ability to release

TNF-α into the blood of an individual does not present a readily usable, real world or well estabilished utility.

Another example (Example 10, page 132] is the asserted utility that the encoded polypeptide may be used as an antigen to make antibodies. Because neither the physiological nor the clinical significance of the polypeptide is disclosed, and because the prior art does not support a very close structural relationship to a disclosed well described family of known proteins disclosed in the specification by both structure and function, the polypeptide and encoding polynucleotide do not have utility as required by 35 USC 101. If the polypeptide antigen does not have utility, then the antibody which binds it (or method of making the antibody) does not have a specific and substantial utility.

Lastly, in Figure 80, it is indicated that the polypeptide has a N-glycosylation and PMP-22/EMP/MP20 family consensus site; however, neither of these sites alone or in combination provides sufficient information for the skilled artisan to readily identify a specific and substantial use for the protein or its encoding polynucleotide.

For these reasons, there is no substantial and specific utility for the claimed polypeptide.

Claims 1-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polynucleotide because no readily usable function or directly associated disease has been determined for the polynucleotide of SEQ ID NO:79, and there is no disclosed definite enabled function supported by the prior art. No function can be reasonably assigned based on its homology to another polynucleotide(s). Using the claimed polynucleotide would require undue experimentation.

Claims 1-6, 9, 10 and 14-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence or which hybridizes to a disclosed sequence. The claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Which nucleic acids of the genus comprising the required sequence are part of the invention has not been set forth.

Other claims are drawn to a nucleic acid encoding specifically the extracellular domain of the polypeptide of SEQ ID NO:80 (with our without its signal sequence), even though no extracellular domain has been described. While a signal peptide was identified as amino acids 1-24 of SEQ ID NO:80, there are three putative transmembrane domain, and it is not clear which intervening sequences if any are extracellular. The specification does not provide information about if the protein is transported to/through the cell's membrane. Similarly, while there is an apparent glycosylation sites, it is not clear if that site is used and its identification does not support the description of an extracellular domain. Therefore, a nucleic acid encoding the extracellular domain has not been described.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides comprising the sequence set forth in SEQ ID NO: 79 (or the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC 203241) with or without its signal sequence, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 9, 10, 14, 15 and dependent claims 7, 8, 11-13 and 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because of the recitation of "extracellular domain". There has been no extracellular domain identified. While a signal peptide was identified as amino acids 1-24 of SEQ ID NO:80, it is unclear where the signal sequence causes the protein to be

transported. Also, there are three putative transmembrane domain, and it is not clear which intervening sequences if any are extracellular. Accordingly, the limitation that the claimed polynucleotide encoding an "extracellular domain" is indefinite.

The metes and bounds of claims 14 and 15 are not clear. Claim 14 is indefinite because because of the recitation: "An isolated nucleic acid that hybridizes to..." What specific conditions are intended for hybridization in the present claim is unknown. What conditions of stringency are used in any particular situation are determined by the specificity of hybridization desired by the practitioner. Simiarly, for claim 15, while the skilled artisan understands the general concept of hybridization under "stringent conditions", what specific conditions are intended by the use of the term "stringent" in the present claims is unknown. In this case, the desired specificity is unknown. If Applicants intend that hybridization under any condition is permissible, even the most permissive allowing non-specific hybridization to occur, then the nucleic acid of this claim reads on almost any nucleic acid. If however, there is a structural relatedness (limitation) that is intended by the hybridization or stringency limitation, then those conditions or range of conditions must be clear in the claim.

35 U.S.C. § 102

The following rejections under 35 U.S.C. § 102 is made under the assumption that the effective filing date for the instantly claimed invention is 05/8/2002, which is the actual filing date of the instant application. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. §120 from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the new claimed invention. Because the instant application does *not* meet the requirements of 35 U.S.C. § 112, first paragraph, for the reasons given above and it is a continuing application of Serial Number 10/006,867, the prior application also does not meet those requirements for the claimed invention and, therefore, is unavailable under 35 U.S.C. § 120.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession AL158821.

GenBank Accession AL158821 teaches human DNA sequence from clone RP1-57H8 that comprises the sequence of SEQ ID NO:79 of the instant application (see included GenBank reference for AL158821 for sequence comparison). Therefore, the GenBank sequence also teaches a polynucleotide encoding the polypeptide of SEQ ID NO:80.

Claims 1-10 and 12-20 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/25825.

WO 99/25825 teaches human secreted protein #53 (SEQ ID NO:186), which is 100% identical to SEQ ID NO:80 of the instant application and is encoded by a polynucleotide 100% identical to the coding region of SEQ ID NO:79 of the instant application (see attached SEQUENCE COMPARISON, including AAX97865 of BLAST protein database search filed 9/17/02 by Applicant). The polynucleotide of WO 99/25825 is a nucleic acid encoding the polypeptide of SEQ ID NO:80. Note, because of the open term "comprising" in claims "lacking" associated signal sequence, full-length sequences are included. Also taught is the polynucleotide within vectors, host cells, including yeast, and operable association of the polynucleotide within a vector to control sequences (p.50, lines 22-26).

Claims 1-10 and 12-20 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/18915.

WO 00/18915.teaches human membrane associated protein HJNCT (SEQ ID NO:3), which is 100% identical to SEQ ID NO:80 of the instant application and is encoded by a polynucleotide 100% identical to the coding region of SEQ ID NO:79 of the instant application (see attached SEQUENCE COMPARISON, including AAA12585 of BLAST protein database

search filed 9/17/02 by Applicant). The polynucleotide of WO 00/18915is a nucleic acid encoding the polypeptide of SEQ ID NO:80. Note, because of the open term "comprising" in claims "lacking" associated signal sequence, full-length sequences are included. Also taught is the polynucleotide within vectors, host cells, including yeast, and operable association of the polynucleotide within a vector to control sequences (p.23, line 20 to p. 24, line13).

Alternative Names

PRO 1356 is also known as Claudin-2, CLD2, CLDN2, UNQ705, HJNCT and SP82, among other names.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The instant protein is 91% identical to mouse claudin-2 (Furuse et al., J. Cell Biol., 141(7):1539, 1998, and attached sequence comparison), which is a four transmembrane protein localized at tight junctions. The claudin superfamily of proteins appears to promote scaffolding of the tight junction transmembrane proteins and a link to the actin cytoskeleton (abstract, Heiskala et al., Traffic 2:92, 2001). Note that the existence of four transmembrane domains in claudins (see above 2 references, Fig. 4 and Fig. 1, respectively), supports the lack of knowledge by the inventors pertaining to what regions of the encoded PRO 1356 protein were extracellular domains. Also, note that a specific and substantial utility (function) of PRO1356 as a claudin-2 protein is not supported in the instant specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

May 12, 2005